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# Brachmann-de Lange Syndrome: Pre- and Postnatal Findings

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**Brachmann-de Lange syndrome (BDLS) is a well-delineated and relatively common syndrome. However, prenatal diagnosis has never been reported, even if in some cases ultrasonography demonstrated one or more manifestations of the syndrome. We report on 3 cases: in the first 2 cases, prenatal ultrasonography demonstrated some signs of the condition. The third represents, to our knowledge, the first prenatal diagnosis of BDLS. We also present a review of the literature concerning pre- and postnatal findings in this syndrome.** © 1996 Wiley-Liss, Inc.

**KEY WORDS: Brachmann-de Lange syndrome, fetus, ultrasound diagnosis, diaphragmatic hernia**

## INTRODUCTION

The Brachmann-de Lange Syndrome (BDLS) is characterized by pre- and postnatal growth and mental retardation, microbrachycephaly, visceral and limb anomalies, hypertrichosis, and characteristic face. It is well-delineated and relatively common (0.6/100,000) [Beck, 1976]. However, prenatal diagnosis has not been reported previously, even if in some cases ultrasonography demonstrated one or more manifestations of the syndrome.

We report on 3 cases of BDLS. One of them was diagnosed on prenatal routine ultrasound examination. In reviewing the literature, we found 7 descriptions of prenatal manifestations of BDLS, but in all of these 7 cases the diagnosis was made after birth.

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## CLINICAL REPORTS

### Case 1

A healthy 19-year-old gravida 2, para 1 woman, married nonconsanguineously, with unremarkable family history, presented for routine ultrasound examination at 32 weeks of gestation. Intrauterine growth retardation (IUGR) and hydramnios were noted. Fetal chromosomes were normal female (46,XX), but soon after amniocentesis fetal death occurred at 34 weeks.

The female fetus was very small for gestational age: weight was 1,000 g, and length was 39 cm (both <3rd centile). Characteristic findings of BDLS were noted (Fig. 1): round face with low hairline, synophris, long eyelashes, a small nose with upturned nostrils, long philtrum, thin upper lip with downturned corners of the mouth, cleft palate, micrognathia, and apparently low-set ears. There was marked hirsutism of the back and limbs. The fetus also presented with hypoplasia of the right forearm and monodactylous right hand.

The autopsy showed no other malformations. On x-rays there were right ulnar aplasia, radial hypoplasia and monodactyly with a single phalanx, and left first metacarpal hypoplasia.

### Case 2

A 29-year-old gravida 5, para 4 woman with unremarkable family history presented for routine ultrasound examination at 32 weeks of gestation. She denied any consanguinity with her husband, and had 4 healthy children. Ultrasound examination demonstrated a fetus with IUGR, bilateral diaphragmatic hernia, abnormalities of the left arm, and hydramnios. Fetal chromosomes were normal (46,XY). After discussion with the parents, the pregnancy was terminated at 33 weeks of gestation.

On examination, the male fetus was small for gestational age: weight was 1,300 g, and length was 38 cm (both <<3rd centile). The face was characteristic of BDLS (Fig. 2), with low hairline and abundant facial hair, small nose, upturned nostrils, synophris, long eyelashes, and hypertrichosis. The fetus also presented with bilateral cryptorchidism, hypoplastic left forearm, cleft hand, and absent right fifth digit.

Fig. 1. Patient 1. Characteristic face of BDLS (round face with low hairline, synophris, long eyelashes, small nose with upturned nostrils, long philtrum, thin upper lip with downturned corners of the mouth, micrognathia, and apparently low-set ears), marked hirsutism of the back and limbs, hypoplasia of the right forearm, and monodactylous right hand.

The autopsy demonstrated bilateral diaphragmatic hernia with lung hypoplasia, left clubhand and oligodactyly, and absence of the fifth right digit. Radiographs showed left ulnar, third, fourth, and fifth left ray aplasia, and right fifth digit aplasia, as well as right first metacarpal hypoplasia and thin rib cortices with undulating appearance.

### Case 3

A 23-year-old gravida 3, para 1, abortus 1 woman with unremarkable family history presented for routine ultrasound examination at 33 weeks of gestation. She was healthy and married nonconsanguineously. Findings on routine ultrasound examinations performed at 12 and 22 weeks were normal. At 33 weeks an additional ultrasound study showed IUGR (biparietal diameter, abdominal circumference, and long bone measurements <10th centile), bilateral limb abnormalities with flexed forearms (probable aplastic ulna), oligodactyly, and heart displacement. A characteristic face noted at the ultrasound examination was noteworthy: severe micrognathia, long bulging philtrum, and small nose with severely depressed nasal bridge (Fig. 3).

BDLS was suspected on the basis of the association of IUGR, limb and visceral abnormalities, and abnormal face. At 33 weeks and 5 days of gestation, the patient developed fever and uterine contractions; after discussion with the parents, the pregnancy was terminated.

The male fetus presented the characteristic BDLS face (Fig. 4) and severe IUGR (weight was 1,300 g, length 39 cm, both <3rd centile).

X-rays confirmed the limb abnormalities with bilateral ulnar aplasia, radial hypoplasia, and oligodactyly: absence of the third, fourth, and fifth rays (Fig. 5), and presence of 13 ribs. The autopsy showed bilateral diaphragmatic hernia, and a small ventricular septal defect. Chromosomes were normal (46,XY).

## DISCUSSION

BDLS is a congenital disorder characterized by a distinct phenotype which includes limb [Braddock et al., 1993] and visceral anomalies, pre- and/or postnatal growth deficiency, mental retardation, and a characteristic face with microbrachycephaly, hirsutism, synophris, long eyelashes, small nose with depressed nasal bridge, long bulging philtrum, thin lips, micrognathia, and apparently low-set ears.

The syndrome is usually sporadic, although autosomal-dominant inheritance with variable expressivity has been suggested [Feingold and Lin, 1993; Van Allen et al., 1993].

We report on 2 cases in which BDLS was diagnosed on anatomical examination after termination of pregnancy (patient 2) or after intrauterine death (patient 1). In both cases, ultrasound examination had noted IUGR, associated in patient 2 with diaphragmatic hernia and limb malformations. In the third case, the diagnosis was made on routine prenatal ultrasound examination performed at 33 weeks of gestation on the basis of the association of severe IUGR, diaphragmatic hernia, upper limb defects, and typical fetal profile.

In all 3 cases, dosage of pregnancy-associated plasma protein (PAPPA) was not performed. Thus we cannot confirm the absence of this large zinc glycoprotein previously observed in maternal serum and placental tissues [Opitz, 1994].

These 3 cases and a review of the literature (Tables I and II) allow us to confirm that diaphragmatic hernia

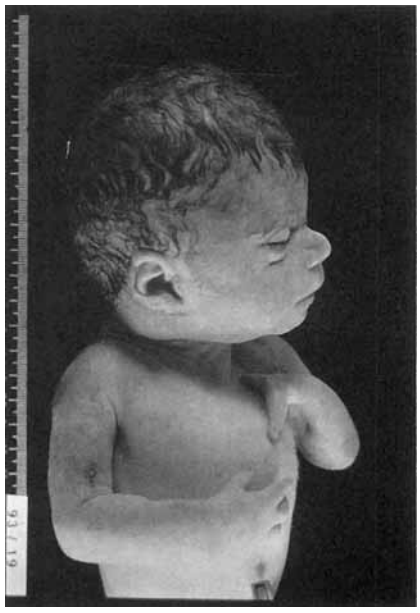

Fig. 2. Patient 2. Typical BDLS face (low hairline and abundant facial hair, small nose, upturned nostrils, synophris, long eyelashes, and hypertrichosis) and left oligodactyly.


Fig. 3. Patient 3. Fetus at 33 weeks of gestation. Typical ultrasonographic profile of BDLS: severe micrognathia, long bulging philtrum, and small nose with severely depressed nasal bridge.

is a frequent finding in severe BDLS, and to specify the ultrasonographic traits which must be sought in the event of IUGR accompanied by limb or visceral malformations. Although 2 previous reports suspected BDLS on ultrasound examination, prenatal diagnosis has never been made based on typical face, severe IUGR, and limb and visceral abnormalities, even if the latter three findings could easily be detected: IUGR seems to be a constant ultrasonographic finding in BDLS [Kliewer et al., 1993], and can sometimes be detected early [Bruner and Hsia, 1990].

Limb anomalies may be difficult to detect, and must be sought carefully [Stoll et al., 1994; Bronstein et al., 1993]. These malformations are more often limited to the upper limbs (ulnar agenesis, oligodactyly, and monodactyly), and are usually asymmetric.

Multiple visceral (cardiac, renal, and gastrointestinal) anomalies occur frequently in BDLS, but are rarely noted prenatally. Diaphragmatic hernia is probably a common manifestation of BDLS and has been noted prenatally in 5 cases [Russel et al., 1993; Cunniff et al., 1993; Pankau and Janig, 1993].

Cystic hygroma has been noted prenatally in 2 cases of BDLS [Drolshagen et al., 1992; Bruner and Hsia, 1990], and may be considered a nonspecific but helpful sign in the prenatal diagnosis of this condition [Kousseff et al., 1994]. Bruner and Hsia [1990] reported on a case in which ultrasound examination performed at 16 weeks of gestation showed cystic hygroma and early-onset IUGR. The fetus, delivered at 35 weeks, had typical BDLS. Ultrasonographically-detected anomaly of the fetal face was described once [Drolshagen et al., 1992]. The fetus presented with ultrasonographic findings such as cystic hygroma, IUGR, and ulnar defect between 12–14 weeks of gestation, and tetralogy of Fallot at 20 weeks. During the third trimester, an abnormal face with thickened skin on the forehead and prominent eyelashes was noted. BDLS was diagnosed neonatally.

## CONCLUSIONS

The detection of diaphragmatic hernia and/or IUGR and/or limb defects on ultrasound examination re-

Fig. 4. Patient 3. Note face typical of BDLS, superposable to the profile ultrasonographically observed, and bilateral limb abnormalities.

TABLE I. Prenatally Detected Findings in BDLS*

| | Drolshagen et al. [1992] | Bruner and Hsia [1990] | Russel et al. [1993] | Cunniff et al. [1993] (case 3) | Cunniff et al. [1993] (case 6) | Cunniff et al. [1993] (case 11) | Pankau and Janig [1993] | Present patient 1 | Present patient 2 | Present patient 3 |
|---|---|---|---|---|---|---|---|---|---|---|
| IUGR | + | + | + | + | ? | ? | + | + | – | + |
| Microcephaly | + | + | – | – | – | – | – | – | – | – |
| Cystic hygroma | + | + | – | – | – | – | – | – | – | – |
| Limb defects | Flexed right upper limb, aplastic ulna | – | Wrist anomalies | – | ? | ? | – | – | Oligodactyly of left upper limb | Bilateral aplastic ulna, oligodactyly |
| Congenital heart defect | Ventricular septal defect, right aortic arch | – | – | – | – | – | – | – | – | – |
| Diaphragmatic hernia | – | – | + | + | + | + | + | – | + | + (heart displacement) |
| Abnormal face | Thick skin on forehead, long eyelashes | – | – | – | – | – | – | – | – | Micrognathia, long bulging philtrum, small nose, depressed nasal bridge |
| Karyotype | 46,XX | 46,XX | 46,XY | 46,XY | 46,XY | 46,XX | ? | 46,XX | 46,XY | 46,XY |

* Please compare with Table II (postnatal findings).

TABLE II. Postnatal Findings in BDLS

| | Drolshagen et al. [1992] | Bruner and Hsia [1990] | Russel et al. [1993] | Cunniff et al. [1993] (case 3) | Cunniff et al. [1993] (case 6) | Cunniff et al. [1993] (case 11) | Pankau and Janig [1993] | Present patient 1 | Present patient 2 | Present patient 3 |
|---|---|---|---|---|---|---|---|---|---|---|
| Gestation and delivery | 41 weeks, induced labor | 34 weeks, cesarean | 39 weeks, cesarean | 36 weeks, cesarean | ? | ? | 36 weeks, cesarean | 33 weeks, intra-uterine death | 33 weeks, terminated pregnancy | 33 weeks, terminated pregnancy |
| Weight (g) | 1,870 | 1,685 | 1,960 | 1,800 | 2,100 | ? | 1,650 | 1,000 | 1,300 | 1,300 |
| Length (cm) | | | 40.5 | 28.5 | | | 39 | 39 | 38 | 39 |
| OFC (cm) | | | 31.5 | | | | 27.5 | | 27 | 26 |
| | | | <10th centile | <5th centile | | | <3rd centile | <3rd centile | <3rd centile | <3rd centile |
| Hirsutism | + | – | + | + | | | + | + | + | + |
| Synophris | ? | + | – | + | | | + | + | + | + |
| Thin lips | ? | + | + | ? | | | ? | + | + | + |
| Small nose | ? | + | – | + | ? | ? | ? | + | + | + |
| Anteverted nostrils | ? | – | + | ? | | | ? | + | + | + |
| Long eyelashes | ? | – | – | + | | | ? | + | + | + |
| Long bulging philtrum | ? | + | – | - | | | | + | + | + |
| Apparently low-set ears | ? | – | – | ? | | | ? | + | + | + |
| Others | | | Small mandible, prominent occiput | Supraorbital ridge hypoplasia | | | | Downturned mouth | | |
| Limb defects | ? | Stubby fingers deep nails | Short arms, right monodactyly, left oligodactyly, nail nail hypoplasia, absent wrists, carpal bones, and radii | Bilateral oligodactyly with thumb hypoplasia | Right ulnar defect | Bilateral ulnar defect | Right: absent ulna and monodactyly Left: oligodactyly | Right: radial hypoplasia, ulnar aplasia monodactyly Left: first metacarpal hypoplasia | Right: first metacarpal hypoplasia Left: ulnar aplasia, 3rd, 4th and 5th ray aplasia | Bilateral: ulnar aplasia, radial hypoplasia, oligodactyly |
| Rib anomalies | – | – | – | – | – | – | – | – | Undulating ribs, thin cortices | 13 ribs |
| Congenital heart defects | Tetralogy of Fallot | Tetralogy of Fallot | – | – | – | + | + | – | – | ventricular septal defect |
| Diaphragmatic hernia | – | – | + | + (left) | + (left) | + (bilateral) | – | –- | + | + (bilateral) |
| Cryptorchidism | | | + (bilateral) | + Hypospadias (bilateral) | | | | | + (bilateral) | + (bilateral) |
| Age at death | 6 months | 10 days | 5 hr | 6 days | < 24 hr | 1 hr | 6 hr | 33 weeks of gestation | 33 weeks of gestation | 33 weeks, 5 days of gestation |

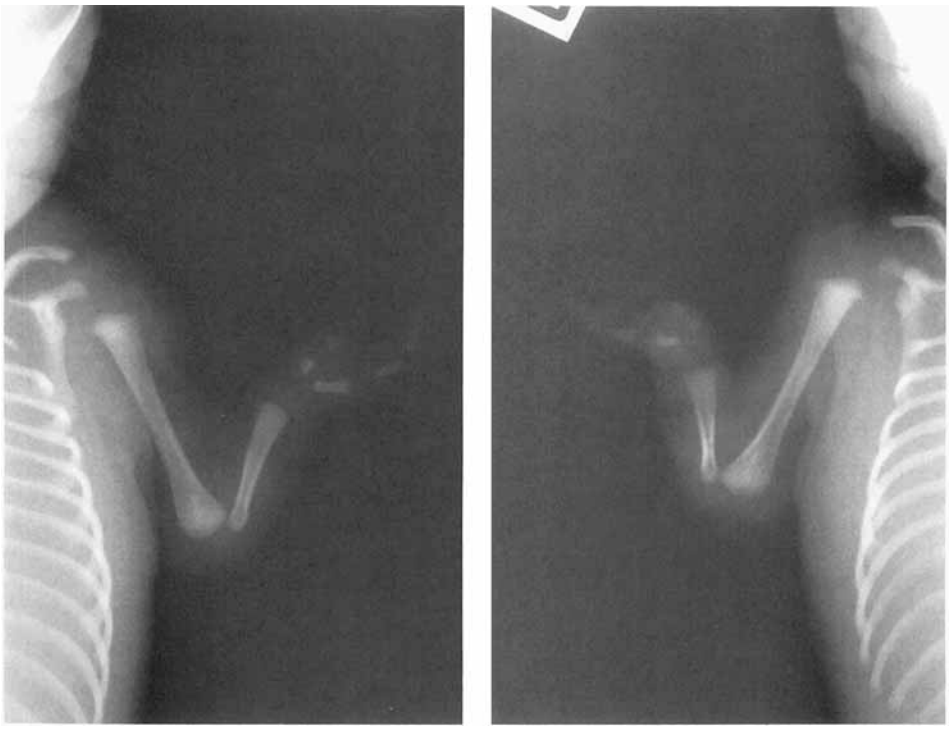

Fig. 5. Patient 3. Radiographs showing bilateral ulnar aplasia and radial hypoplasia, oligodactyly with absence of third, fourth, and fifth rays, and presence of 13 ribs.

quires a careful search for other abnormalities, including a typical fetal profile [Turner and Twining, 1993], leading to the diagnosis of BDLS. One should also bear in mind that similar anomalies are observed in partial duplication 3q, leading to differential diagnosis with this rare chromosomal anomaly, and requiring a cytogenetic investigation [Holder et al., 1994].

As BDLS entails a high risk of mortality during the first year for the most severely affected infants [Drolshagen et al., 1992], and severe mental retardation in most surviving patients, precise prenatal diagnosis is important for clinical management of the pregnancy.

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